Name: Aritra Bhattacherjee Email: aritra.bhattacherjee@childrens.harvard.edu
PI Name: Yi Zhang PI Email: yzhang@genetics.med.harvard.edu

Decoding molecular organization of the brain reward circuit for understanding mechanisms of drug addiction

Aritra Bhattacherjee, Zheng-dong Zhao, Chao Zhang, Renchao Chen, Nadhir Djekidel, Jeffrey Moffitt, Yi Zhang

Boston Children's Hospital, Harvard Medical School, Howard Hughes Medical Institute

Drug addiction is a complex disorder believed to involve molecular changes in multiple neural circuits associated with the brain reward system. Decoding these adaptive changes across diverse circuits, composed of numerous molecularly heterogeneous neuron subtypes, is the central challenge in understanding drug addiction. Over the past few years, we have taken a comprehensive approach to systematically decode the molecular profile and spatial organization of all heterogeneous cell types in the nucleus accumbens (NAc) and the prefrontal cortex (PFC), the two principal brain regions regulating drug addiction. We find that organization of molecularly discrete cell types in these regions follow anatomically distinct principles that recapitulate subregion demarcations and biological functions; and exhibit heterogeneous responses to drugs of abuse. Based on this knowledge, we have mapped circuits and generated several neuron subtype-specific Cre mouse lines to fully decode the molecular underpinnings of drug addiction. In NAc, we recently discovered that activating a molecularly distinct subtype of D1 MSN (Tac2+) in the shell region, inhibits drug taking in intravenous self-administration mouse model (contrary to a general assumption that D1 neurons promote drug taking). Multiple studies are currently underway evaluating drug- and/or stage-specific recruitment of molecularly defined NAc and PFC circuits during the inception and progression of addiction. Cumulatively, our efforts are focused towards a complete decoding of the molecularly defined circuits that stage-specifically engage during the progression of drug addiction, and identifying (and eventually reversing) the adaptive changes undergone by these neurons during transition to compulsive drug taking.